Human oligoclonal recombinant antivenom against the black mamba (Dendroaspis polylepis)

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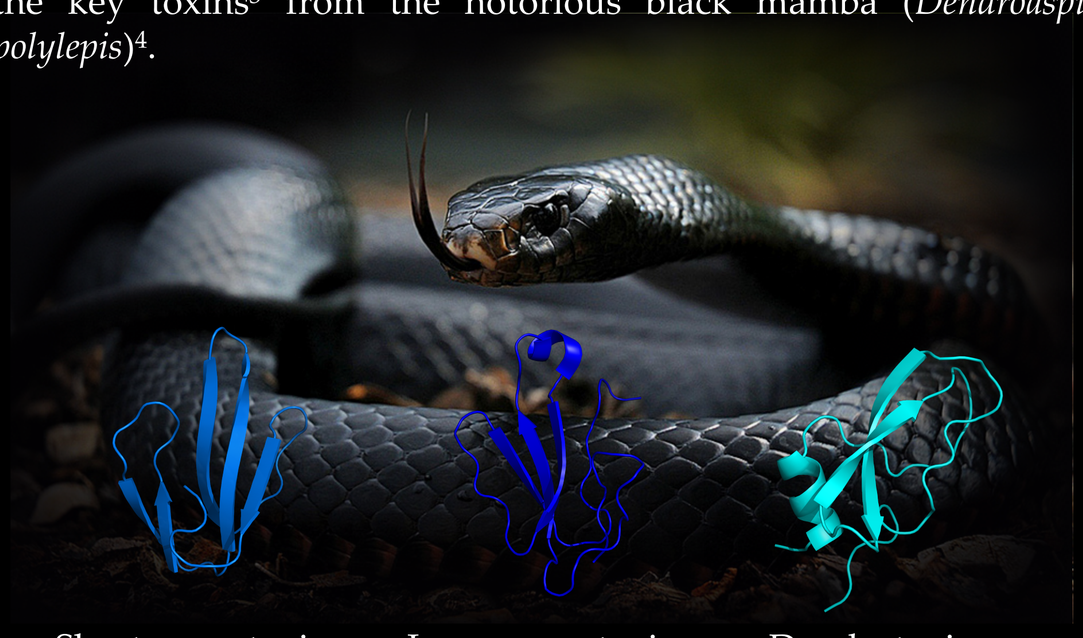
Snakebite: a neglected tropical disease

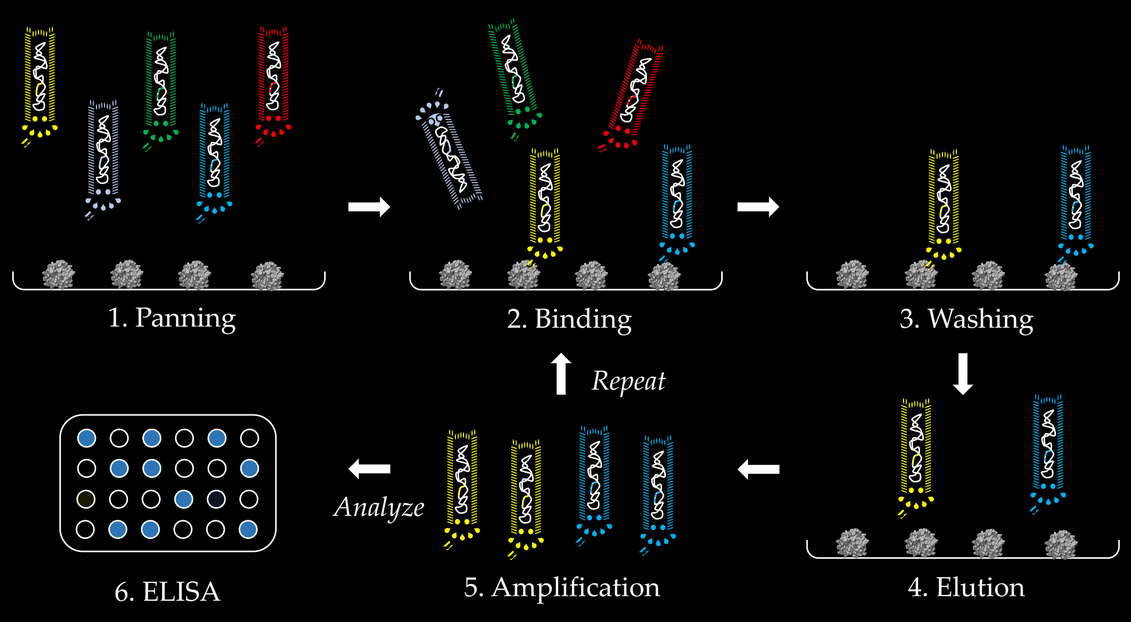
Snakebite envenoming is a major cause of death and morbidity in tropical parts of the world. Current therapies are based on animal-derived antisera that are associated with a high degree of immunogenicity, high cost, and batch-to-batch variation[1,2]. Here, we report the results of our ongoing efforts of developing the world's first fully recombinant antivenom based on human IgGs targeting the key toxins[3] from the notorious black mamba (*Dendroaspis polylepis*)[4].



Short neurotoxin Long neurotoxin Dendrotoxin

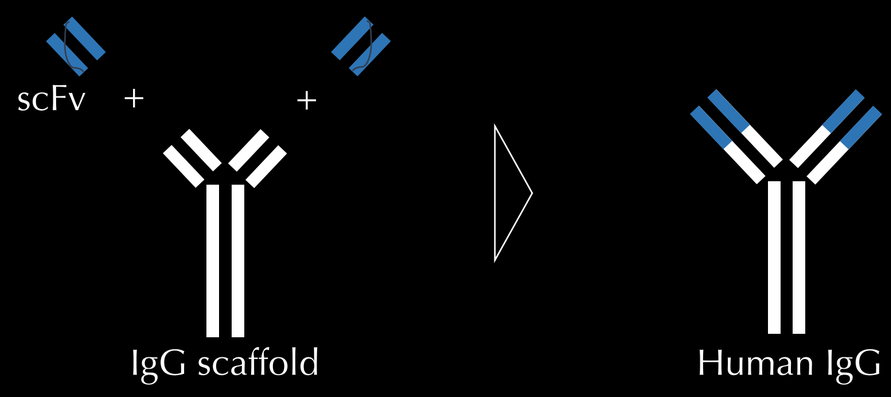
Discovery of human scFvs by phage display

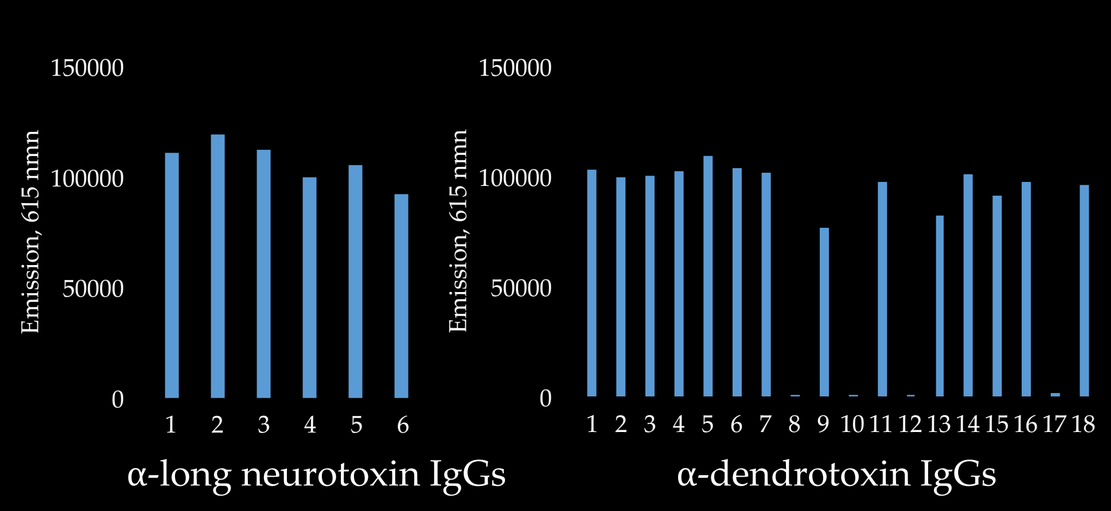
Based on a combined toxicovenomics and phage display selection approach[5], 431 human scFv binders were isolated from a phage display library against the medically relevant neurotoxins and dendrotoxins of *D. polylepis*.



Conversion of unique scFv binders to IgG

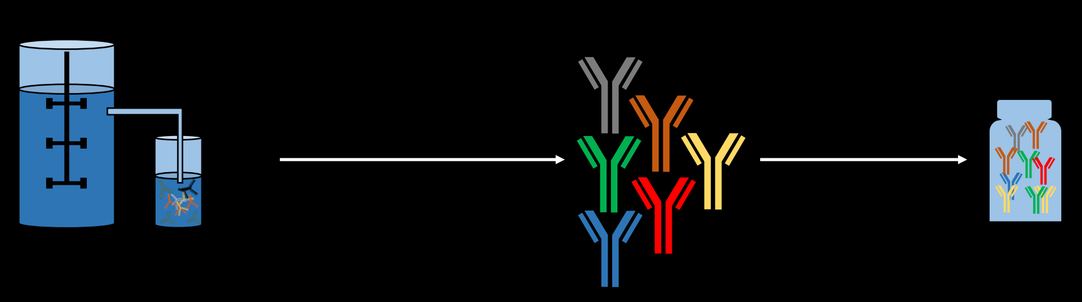
Following expression of 147 scFvs with unique V_H CDR3 regions in *E. coli* and evaluation of binding strength, the 24 most promising scFvs were selected and converted to IgG format. Of these, 20 displayed good binding after successful expression in HEK cells.





Human oligoclonal recombinant antivenoms

Currently, the binding affinities and the neutralization potential of these 20 toxin-targeting IgGs is being investigated with the aim of being able to design a cost-effective recombinant oligoclonal mixture of IgGs[6] that can effectively neutralize the lethal effects of the synergistically-acting venom of *D. polylepis*[7].



Oligoclonal expression of human IgGs

References

[1] Gutiérrez JM, León G, Lomonte B, Angulo Y. In-flammation & Allergy-Drug Targets 2011, 10; p369-80.
[2] Laustsen AH, Engmark M, Milbo C, Johannesen J, Lomonte B, Gutiérrez JM, Lohse B. Current Pharmaceutical Design 2016, 22.
[3] Laustsen AH, Lohse B, Lomonte B, Engmark M, Gutiérrez JM. Toxicon 2015, 104; p43-45.
[4] Laustsen AH, Lomonte B, Lohse B, Fernández J, Gutiérrez JM. Journal of Proteomics 2015, 119; p126-142.
[5] Laustsen AH. Recombinant Antivenoms. University of Copenhagen 2016.
[6] Laustsen AH, Johansen KH, Engmark M, Andersen MR. Nature 2016, 538; p41.
[7] Laustsen AH. Toxin Reviews 2016, 35; p165-170.

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